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NEWS	7	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS	8	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements
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NEWS	14	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS	15	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS	16	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS	17	MAR 31	LPCI now available as a replacement to LDPCI
NEWS	18	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS	19	APR 04	STN AnaVist, Version 1, to be discontinued
NEWS	20	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS	21	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS	22	APR 28	IMSRESEARCH reloaded with enhancements

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NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

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=> s (mpt or mitochondrial permeability transition) and superoxide
L1         261 (MPT OR MITOCHONDRIAL PERMEABILITY TRANSITION) AND SUPEROXIDE

=> s l1 and py<=2001
L2          90 L1 AND PY<=2001

=> dup rem l
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session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           51 DUP REM L2 (39 DUPLICATES REMOVED)

=> s l3 and (cellular or intracellular)
L4          19 L3 AND (CELLULAR OR INTRACELLULAR)

=> d l4 ibib abs 1-19

L4   ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2002:527735  CAPLUS
DOCUMENT NUMBER:         137:308088
TITLE:                   A mitochondrial paradigm for degenerative diseases and
                         ageing
AUTHOR(S):               Wallace, Douglas C.
CORPORATE SOURCE:        Center for Molecular Medicine, Emory University,
                         Atlanta, GA, 30322, USA
SOURCE:                  Novartis Foundation Symposium (2001),
                         235(Aging Vulnerability), 247-266
                         CODEN: NFSYF7; ISSN: 1528-2511
PUBLISHER:               John Wiley & Sons Ltd.
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                English
AB   A review.  A variety of degenerative diseases have now been shown to be
     caused by mutations in mitochondrial genes encoded by the mtDNA or the
     nuclear DNA (nDNA).  The mitochondria generate most of the
     cellular energy by oxidative phosphorylation (OXPHOS), and produce
     most of the toxic reactive oxygen species (ROS) as a byproduct.  Genetic
     defects that inhibit OXPHOS also cause the redirection of OXPHOS electrons
     into ROS production, thus increasing oxidative stress.  A decline in
     mitochondrial energy production and an increase in oxidative stress can
     impinge on the mitochondrial permeability
```

transition pore (mtPTP) to initiate programmed cell death (apoptosis). The interaction of these three factors appear to play a major role on the pathophysiol. of degenerative diseases. Inherited diseases can result from mtDNA base substitution and rearrangement mutations and can affect the CNS, heart and skeletal muscle, and renal, endocrine and hematol. systems. In addition, somatic mtDNA mutations accumulate with age in post-mitotic tissues in association with the age-related decline in mitochondrial function and are thought to be an important factor in aging and senescence. The importance of mitochondrial defects in degenerative diseases and aging has been demonstrated using mouse models of mitochondrial disease. An mtDNA mutation imparting chloramphenicol resistance (CAPR) to mitochondrial protein synthesis has been transferred into mice and resulted in growth retardation and cardiomyopathy. A nDNA mutation which inactivates the heart-muscle isoform of the adenine nucleotide translocator (Anti) results in mitochondrial myopathy and cardiomyopathy; induction of ROS production; the compensatory up-regulation of energy, antioxidant, and apoptosis gene expression; and an increase in the mtDNA somatic mutation rate. Finally, a nDNA mutation which inactivates the mitochondrial Mn superoxide dismutase (MnSOD) results in death in about 8 days due to dilated cardiomyopathy, which can be ameliorated by treatment with catalytic anti-oxidants. A partial MnSOD deficiency chronically increases oxidative stress, decreases OXPHOS function, and stimulates apoptosis. Thus, the decline of mitochondrial energy production resulting in increased oxidative stress and apoptosis does play a significant role in degenerative diseases and aging.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:774174 CAPLUS

DOCUMENT NUMBER: 136:384182

TITLE: Early vacuolization and mitochondrial damage in motor neurons of FALS mice are not associated with apoptosis or with changes in cytochrome oxidase histochemical reactivity

AUTHOR(S): Bendotti, Caterina; Calvaresi, Novella; Chiveri, Luca; Prelle, Alessandro; Moggio, Maurizio; Braga, Massimilano; Silani, Vincenzo; De Biasi, Silvia

CORPORATE SOURCE: Department of Neuroscience, Laboratory of Molecular Neurobiology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy

SOURCE: Journal of the Neurological Sciences (2001), 191(1-2), 25-33
CODEN: JNSCAG; ISSN: 0022-510X

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Overexpression of mutated superoxide dismutase (SOD1) in transgenic mice causes a progressive motor neuron degeneration in the spinal cord similar to that in human amyotrophic lateral sclerosis (ALS). Ultrastructural anal. of motor neurons at different stages of the disease in transgenic C57BL/6 mice carrying the G93A mutation of SOD1 showed, at about 2 wk of age, much earlier than the initial symptoms of the disease, microvacuoles in the cytoplasm, with marked swelling of the mitochondria. Nuclei with an apoptotic morphol. were never observed in these motor neurons. Swollen mitochondria were also seen in the distal part of motor axons of phrenic nerves and in the large axons of sciatic nerves before the onset of the disease, but no mitochondrial alterations were seen in skeletal muscles or in the small sciatic nerve axons. Moreover, we found no apparent changes in the histochem. reactivity of cytochrome oxidase in motor neurons of transgenic mice even at the advanced stage of the

disease, suggesting that partial neuronal activity in these cells may be maintained despite the altered mitochondria. Immunoreactivity for human SOD1 was high around vacuoles in the motor neurons of transgenic mice but no cytoplasmic intracellular SOD1 aggregates were observed Our data indicate that mitochondrial swelling may be an important factor triggering the cascade leading to progressive motor neuron death. Activation of the mitochondrial permeability transition pore may be involved in this process, through excitotoxicity or other neurotoxic stimuli.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:471010 CAPLUS

DOCUMENT NUMBER: 135:209779

TITLE: Induction of apoptosis in human T cells by Actinobacillus actinomycetemcomitans cytolethal distending toxin is a consequence of G2 arrest of the cell cycle

AUTHOR(S): Shenker, Bruce J.; Hoffmaster, Roselle H.; Zekavat, Ali; Yamaguchi, Noboru; Lally, Edward T.; Demuth, Donald R.

CORPORATE SOURCE: Department of Pathology, University of Pennsylvania School of Dental Medicine, Philadelphia, PA, 19104, USA

SOURCE: Journal of Immunology (2001), 167(1), 435-441
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have previously shown that Actinobacillus actinomycetemcomitans produces an immunosuppressive factor that is encoded by the cdtB gene, which is homologous to a family of cytolethal distending toxins (Cdt) expressed by several Gram-neg. bacteria. Moreover, the authors have shown that CdtB impairs lymphocyte function by inducing G2 arrest of the cell cycle. The authors now report that both CdtB as well as an extract prepared from an Escherichia coli strain that expresses all three of the A. actinomycetemcomitans cdt genes (rCdtABC) induce apoptosis. Pretreatment of lymphocytes with either CdtB or rCdtABC leads to DNA fragmentation in activated lymphocytes at 72 and 96 h. No DNA fragmentation was induced in nonactivated cells. Flow cytometric anal. of the Cdt-treated lymphocytes demonstrates a reduction in cell size and an increase in nuclear condensation. Mitochondrial function was also perturbed in cells pretreated with either CdtB or rCdtABC. An increase in the expression of the mitochondria Ag, Apo 2.7, was observed along with evidence of the development of a mitochondrial permeability transition state; this includes a decrease in the transmembrane potential and elevated generation of reactive oxygen species. Activation of the caspase cascade, which is an important biochem. feature of the apoptotic process, was also observed in Cdt-treated lymphocytes. Overexpression of the bcl-2 gene in the human B lymphoblastoid cell line, JY, led to a decrease in Cdt-induced apoptosis. Interestingly, Bcl-2 overexpression did not block Cdt-induced G2 arrest. The implications of the results with respect to the immunosuppressive functions of Cdt proteins are discussed.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:340937 CAPLUS

DOCUMENT NUMBER: 135:42088

TITLE: Reactive Oxygen Species and Mitochondria Mediate the Induction of Apoptosis in Human Hepatoma HepG2 Cells by the Rodent Peroxisome Proliferator and Hepatocarcinogen, Perfluorooctanoic Acid
AUTHOR(S): Panaretakis, Theoharis; Shabalina, Irina G.; Grander, Dan; Shoshan, Maria C.; DePierre, Joseph W.
CORPORATE SOURCE: Unit of Biochemical Toxicology, Department of Biochemistry, Wallenberg Laboratory, Stockholm University, Stockholm, S-106 91, Swed.
SOURCE: Toxicology and Applied Pharmacology (2001), 173(1), 56-64
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously shown that one of the most potent rodent hepatocarcinogens, perfluorooctanoic acid (PFOA), induces apoptosis in human Hep G2 cells in a dose- and time-dependent manner. In this study, the authors have investigated the involvement of reactive oxygen species (ROS), mitochondria, and caspase-9 in PFOA-induced apoptosis. Treatment with 200 and 400 μM PFOA was found to cause a dramatic increase in the cellular content of superoxide anions and hydrogen peroxide after 3 h. Measurement of the mitochondrial transmembrane potential (ΔΨm) after PFOA treatment showed a dissipation of ΔΨm at 3 h. Caspase-9 activation was seen at 5 h after treatment with 200 μM PFOA. In order to evaluate the importance of these events in PFOA-induced apoptosis, cells were cotreated with PFOA and N-acetylcysteine (NAC), a precursor of glutathione, or cyclosporin A (CsA), an inhibitor of mitochondrial permeability transition pore (MPT pore). NAC reduced ΔΨm dissipation, caspase 9 activation, and apoptosis, indicating a role for PFOA-induced ROS. In addition, CsA also reduced ΔΨm dissipation, caspase 9 activation, and apoptosis, indicating a role for PFOA-induced opening of the MPT pore. In summary, the authors have delineated a ROS and mitochondria-mediated pathway for the induction of apoptosis by PFOA. (c) 2001 Academic Press.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:81154 CAPLUS
DOCUMENT NUMBER: 134:191262
TITLE: Oxidation of pyridine nucleotides during Fas- and ceramide-induced apoptosis in Jurkat cells: correlation with changes in mitochondria, glutathione depletion, intracellular acidification and caspase 3 activation
AUTHOR(S): Petit, Patrice Xavier; Gendron, Marie-Claude; Schrantz, Nicolas; Metivier, Didier; Kroemer, Guido; Maciorowska, Zofia; Sureau, Franck; Koester, Steven
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire, INSERM U129, CHU Cochin Port-Royal, Paris, F-75014, Fr.
SOURCE: Biochemical Journal (2001), 353(2), 357-367
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Jurkat T cells showed a major, early decrease in blue autofluorescence in response to Fas/Apo-1/CD95 crosslinking or stimulation with cell-permeant ceramide. This indicates the oxidation/depletion of NADH or NADPH before the onset of apoptosis. Kinetic studies, cytofluorimetric multiparameter analyses and cell sorting expts. indicated a close temporal relationship

between NAD(P)H oxidation/depletion and the dissipation of the mitochondrial transmembrane potential (Δψm). In contrast, NAD(P)H depletion was detected well before several other changes associated with late apoptosis, including enhanced superoxide generation, phosphatidylserine exposure on the cell surface, loss of cytosolic K+, decreased cytoplasmic pH, nuclear DNA fragmentation, cell shrinkage, loss of viability and the appearance of the mitochondrial antigen APO2.7. Full activation of caspase 9 and caspase 3 appeared to be correlated with the appearance of superoxide anions in the mitochondria, and followed the drop in NADPH. Overexpression of the apoptosis-inhibitory proto-oncogene Bcl-2, which encodes an inhibitor of the mitochondrial permeability transition (PT) pore, delayed both the Δψm disruption and the depletion of NAD(P)H. Similar effects were observed with the pharmacol. PT pore inhibitors, bongkrekic acid and cyclosporin A. Thus there appears to be a close functional relationship between mitochondrial and cellular redox changes during early apoptosis; events that are inhibited by Bcl-2.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:61092 CAPLUS

DOCUMENT NUMBER: 134:246998

TITLE: Intracellular acidification triggered by mitochondrial-derived hydrogen peroxide is an effector mechanism for drug-induced apoptosis in tumor cells

AUTHOR(S): Hirpara, Jayshree L.; Clement, Marie-Veronique; Pervaiz, Shazib

CORPORATE SOURCE: Department of Physiology, National University of Singapore, Singapore, 119260, Singapore

SOURCE: Journal of Biological Chemistry (2001), 276(1), 514-521
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We recently showed that two photoproducts of merocyanine 540, C2 and C5, triggered cytochrome C release; however, C5 was inefficient in inducing caspase activity and apoptosis in leukemia cells, unlike C2. Here we show that HL60 cells acidified upon exposure to C2 but not C5. The intracellular drop in pH and caspase activation were dependent upon hydrogen peroxide production, and were inhibited by scavengers of hydrogen peroxide. On the contrary, caspase inhibitors did not block hydrogen peroxide production In turn, increased intracellular hydrogen peroxide concentration was downstream of superoxide anion produced within 2 h of exposure to C2. Inhibitor of NADPH oxidase diphenyleneiodonium neither inhibited superoxide production nor caspase activation triggered by C2. However, exposure of purified mitochondria to C2 resulted in significantly increased superoxide production Furthermore, cytochrome C release from isolated mitochondria induced by C2 was completely inhibited in the presence of scavengers of hydrogen peroxide. Contrarily, scavenging hydrogen peroxide had no effect on the cyclosporin A-sensitive mitochondrial permeability transition induced by C5. Our data suggest a scenario where drug-induced hydrogen peroxide production induces intracellular acidification and release of cytochrome C, independent of the inner membrane pore, thereby creating an intracellular environment permissive for caspase activation.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:57967 CAPLUS
DOCUMENT NUMBER: 134:261000
TITLE: Mitochondrial dysfunction after aerobic exposure to the hypoxic cytotoxin tirapazamine
AUTHOR(S): Wouters, Bradly G.; Delahoussaye, Yvette M.; Evans, James W.; Birrell, Geoffrey W.; Dorie, Mary Jo; Wang, Jingli; MacDermed, Dhara; Chiu, Roland K.; Brown, J. Martin
CORPORATE SOURCE: Cancer Research Group, Ottawa Regional Cancer Centre, Ottawa, ON, K1H 8L6, Can.
SOURCE: Cancer Research (2001), 61(1), 145-152
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tirapazamine (TPZ) is a bioreductive drug that exhibits a high degree of selective toxicity toward hypoxic cells, and at doses that are used clin., little or no cell killing is observed in aerobic cells. Nonetheless, the effects of TPZ on aerobic tissues are still responsible for the dose limitations on the clin. administration of this drug. Clin. side effects include fatigue, muscle cramping, and reversible ototoxicity. We have investigated TPZ-induced changes in the mitochondria in aerobically exposed cells as a potential mediator of these side effects. Our data show that aerobic administration of TPZ at clin. relevant doses results in a profound loss in the mitochondrial membrane potential (MMP). We show that loss in the MMP occurs in a variety of cell lines in vitro and also occurs in muscle tissues in vivo. The loss in MMP is temporary because recovery occurs within 2 h. TPZ is directly metabolized within mitochondria to a DNA-damaging form, and this metabolism leads to both the cell-killing effects of TPZ on aerobic cells at high doses and to the loss in MMP at clin. relevant doses. Using cell lines derived from genetically modified mice with a targeted deletion in manganese superoxide dismutase, we have further distinguished the phenotypic effects of TPZ in mitochondria at high toxic doses vs. those at clin. relevant doses. We have investigated several potential mechanisms for this TPZ-induced loss in MMP. Our results indicate no change in the rate of cellular respiration in TPZ-treated cells. This implies that the loss in MMP results from an inability of the inner mitochondrial membrane to sustain a potential across the membrane after TPZ treatment. Incubation of cells with an inhibitor of the mitochondrial permeability transition suggests that the loss of MMP may result from the regulated opening of a large mitochondria channel.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:895969 CAPLUS
DOCUMENT NUMBER: 134:206158
TITLE: Superoxide radical-initiated apoptotic signalling pathway in selenite-treated HepG2 cells: mitochondria serve as the main target
AUTHOR(S): Shen, H.-M.; Yang, C.-F.; Ding, W.-X.; Liu, J.; Ong, C.-N.
CORPORATE SOURCE: Department of Community, Occupational, and Family Medicine, Faculty of Medicine, National University of Singapore, Singapore
SOURCE: Free Radical Biology & Medicine (2001), 30(1), 9-21
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The exact role of superoxide radicals (O2•-) in apoptosis is still a matter of debate. The main objective of the present study is to evaluate the apoptotic signaling pathway initiated by O2•-. The reductive reaction of sodium selenite with glutathione was used as the intracellular O2•--generating system. When cells were exposed to 5 to 25 μM selenite, a temporal pattern of apoptotic events was observed following the elevation of O2•-, in which cytochrome c release and mitochondrial depolarization preceded caspase-3 activation and DNA fragmentation. The simultaneous treatment with N-acetylcysteine and 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl markedly reduced O2•- level and suppressed the mitochondrial changes and the downstream apoptotic events. Moreover, pretreatment with cyclosporin A plus trifluoperazine, two mitochondrial permeability transition (MPT) inhibitors, was capable of attenuating O2•--mediated cytochrome c release and mitochondrial depolarization, and subsequently inhibiting apoptosis. Thus, the present results provide convincing evidence that O2•- generated from the reductive reaction of selenite with GSH is capable of triggering a mitochondria-dependent apoptotic pathway. Such knowledge may not only help to obtain a better understanding of the apoptotic effect of selenite per se, but of the role of O2•- in initiation and execution of apoptosis.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:578290 CAPLUS

DOCUMENT NUMBER: 133:264507

TITLE: Veratridine induces apoptotic death in bovine chromaffin cells through superoxide production

AUTHOR(S): Jordan, Joaquin; Galindo, Maria F.; Calvo, Soledad; Gonzalez-Garcia, Carmen; Cena, Valentin

CORPORATE SOURCE: Institute for Neurosciences University, Alicante, Spain

SOURCE: British Journal of Pharmacology (2000), 130(7), 1496-1504
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1. The mol. mechanisms involved in veratridine-induced chromaffin cell death have been explored. 2. We have found that exposure to veratridine (30 μM, 1 h) produces a delayed cellular death that reaches 55% of the cells 24 h after veratridine exposure. This death has the features of apoptosis as DNA fragmentation can be observed 3. Calcium ions play an important role in veratridine-induced chromaffin cell death because the cell permeant Ca2+ chelator BAPTA-AM and extracellular Ca2+ removal completely prevented veratridine-induced toxicity. 4. Following veratridine treatment, there is a decrease in mitochondrial function and an increase in superoxide anion production Veratridine-induced increase in superoxide production was blocked by tetrodotoxin (TTX; 10 μM), extracellular Ca2+ removal and the mitochondrial permeability transition pore blocker cyclosporine A (10 μM). 5. Veratridine-induced death was prevented by different antioxidant treatments including catalase (100 IU ml-1), N-acetyl cysteine (100 μM), allopurinol (100 μM) or vitamin E (50 μM). 6. Veratridine-induced DNA fragmentation was prevented by TTX (10 μM). 7. Veratridine produced a time-dependent increase in caspase activity that was prevented by Ca2+ removal and TTX (10 μM). In addition, calpain and caspases inhibitors partially prevented veratridine-induced death. 8. These results indicate that chromaffin cells share with neurons the mol.

machinery involved in apoptotic death and might be considered a good model to study neuronal death during neurodegeneration.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:545960 CAPLUS
DOCUMENT NUMBER: 133:290755
TITLE: Intracellular Thiol Depletion Causes Mitochondrial Permeability Transition in Ebselen-Induced Apoptosis
AUTHOR(S): Yang, Cheng Feng; Shen, Han Ming; Ong, Choon Nam
CORPORATE SOURCE: Department of Community, Occupational and Family Medicine, National University of Singapore, 117597, Singapore
SOURCE: Archives of Biochemistry and Biophysics (2000), 380(2), 319-330
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ebselen, a selenoorg. compound, has recently been shown to display a novel property of inducing apoptosis through rapid depletion of intracellular thiols in human hepatoma cells, HepG2. The present study was thus designed to explore the mechanism of how ebselen triggers apoptosis upon depletion of intracellular thiols. The results demonstrated that ebselen treatment triggered mitochondrial permeability transition rather rapidly as revealed by redistribution of calcein green fluorescence from cytosol into mitochondria. Ebselen treatment also caused a dose- and time-dependent loss of mitochondrial membrane potential (MMP) and release of cytochrome c. Pretreatment with N-acetylcysteine, a precursor of intracellular reduced glutathione (GSH) synthesis, significantly attenuated the ebselen-induced MMP disruption and subsequently inhibited the apoptosis. In contrast, pretreatment with buthionine sulfoximine, a specific inhibitor of intracellular GSH synthesis, significantly augmented the ebselen-induced MMP alteration, and enhanced the apoptosis. Although ebselen treatment significantly increased the intracellular superoxide radical and calcium concns., superoxide dismutase, and BAPTA (a calcium chelator), however, failed to prevent ebselen-induced MMP loss and apoptosis. Neither caspase-9 nor caspase-3 activation was detected in ebselen-treated cells. Z-VAD-FMK, a general caspase inhibitor, also had no effect on ebselen-induced MMP decrease and apoptosis. The overall findings thus suggest that mitochondrial permeability transition resulted from intracellular thiol depletion is a critical event in ebselen-induced apoptosis. (c) 2000 Academic Press.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:269879 CAPLUS
DOCUMENT NUMBER: 133:28856
TITLE: Synergistic depletion of astrocytic glutathione by glucose deprivation and peroxynitrite: correlation with mitochondrial dysfunction and subsequent cell death
AUTHOR(S): Ju, Chung; Yoon, Keum-Na; Oh, Yu-Kyoung; Kim, Hyoung-Chun; Shin, Chan Young; Ryu, Jae Ryun; Ko, Kwang Ho; Kim, Won-Ki
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, Ewha Women's University, Seoul, 158-056, S. Korea

SOURCE: Journal of Neurochemistry (2000), 74(5), 1989-1998
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previously, we reported that immunostimulated astrocytes were highly vulnerable to glucose deprivation. The augmented death was mimicked by the peroxynitrite (ONOO-)-producing reagent 3-morpholinosydnonimine (SIN-1). Here, we show that glucose deprivation and ONOO- synergistically deplete intracellular reduced glutathione (GSH) and augment the death of astrocytes via formation of cyclosporin A-sensitive mitochondrial permeability transition (MPT) pore. Astrocytic GSH levels were only slightly decreased by glucose deprivation or SIN-1 (200 μM) alone. In contrast, a rapid and large depletion of GSH was observed in glucose-deprived/SIN-1-treated astrocytes. The depletion of GSH occurred before a significant release of lactate dehydrogenase (a marker of cell death). Superoxide dismutase and ONOO- scavengers completely blocked the augmented death, indicating that the reaction of nitric oxide with superoxide to form ONOO- was implicated. Furthermore, nitrotyrosine immunoreactivity (a marker of ONOO-) was markedly enhanced in glucose-deprived/SIN-1-treated astrocytes. Mitochondrial transmembrane potential (MTP) was synergistically decreased in glucose-deprived/SIN-1-treated astrocytes. The glutathione synthase inhibitor L-buthionine-(S,R)-sulfoximine markedly decreased the MTP and increased lactate dehydrogenase (LDH) releases in SIN-1-treated astrocytes. Cyclosporin A, an MPT pore blocker, completely prevented the MTP depolarization as well as the enhanced LDH releases in glucose-deprived/SIN-1-treated astrocytes.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:424083 CAPLUS
DOCUMENT NUMBER: 131:198568
TITLE: Death signals from the B cell antigen receptor target mitochondria, activating necrotic and apoptotic death cascades in a murine B cell line, WEHI-231
AUTHOR(S): Doi, Toshio; Motoyama, Noboru; Tokunaga, Akinori; Watanabe, Takeshi
CORPORATE SOURCE: Department of Molecular Immunology, Medical Institute of Bioregulation, Kyushu University, Fukuoka, 812-8582, Japan
SOURCE: International Immunology (1999), 11(6), 933-941
CODEN: INIMEN; ISSN: 0953-8178
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB B cell antigen receptor (BCR)-mediated cell death has been proposed as a mechanism for purging the immune repertoire of anti-self specificities during B cell differentiation in bone marrow. Mitochondrial alterations and activation of caspases are required for certain aspects of apoptotic cell death, but how the mitochondria and caspases contribute to BCR-mediated cell death is not well understood. In the present study, we used the mouse WEHI-231 B cell line to demonstrate that mitochondrial alterations and activation of caspases are indeed participants in BCR-mediated cell death. The peptide inhibitor of caspases, N-benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone (z-VAD-fmk), blocked cleavage of poly(ADP-ribose) polymerase and various manifestation of nuclear apoptosis such as nuclear fragmentation, hypodiploidy and DNA fragmentation, indicating that signals from the BCR induced the activation

of caspases. In addition, z-VAD-fmk delayed apoptosis-associated changes in cellular reduction-oxidation potentials as determined by hypergeneration of superoxide anion, as well as exposure of phosphatidylserine residues in the outer plasma membrane. By contrast, although z-VAD-fmk retarded cytolysis, it was incapable of preventing disruption of the plasma membrane even under the same condition in which it completely blocked nuclear apoptosis. Mitochondrial membrane potential loss was also not blocked by z-VAD-fmk. Bongkrekic acid, a specific inhibitor of mitochondrial permeability transition pores, suppressed not only the mitochondrial membrane potential but also the change of plasma membrane permeability. Overexpression of Bcl-xL prevented mitochondrial dysfunction, nuclear apoptosis and membrane permeability cell death triggered by BCR signal transduction. These observations indicate that death signals from BCR may first cause mitochondrial alterations followed by activation of both necrotic and apoptotic cascades.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:246800 CAPLUS

DOCUMENT NUMBER: 131:43160

TITLE: Influence of calcium and iron on cell death and mitochondrial function in oxidatively stressed astrocytes

AUTHOR(S): Robb, S. J.; Robb-Gaspers, L. D.; Scaduto, R. C., Jr.; Thomas, A. P.; Connor, J. R.

CORPORATE SOURCE: George M. Leader Family Laboratory, Department of Neuroscience and Anatomy, M.S. Hershey Medical Center, The Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA

SOURCE: Journal of Neuroscience Research (1999), 55(6), 674-686
CODEN: JNREDK; ISSN: 0360-4012

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Astrocytes protect neurons and oligodendrocytes by buffering ions, neurotransmitters, and providing metabolic support. However, astrocytes are also vulnerable to oxidative stress, which may affect their protective and supportive functions. This paper examines the influence of calcium and iron on astrocytes and dets. if cell death could be mediated by mitochondrial dysfunction. The authors provide evidence that the events associated with peroxide-induced death of astrocytes involves generation of superoxide at the site of mitochondria, loss of mitochondrial membrane potential, and depletion of ATP. These events are iron-mediated, with iron loading exacerbating and iron chelation reducing oxidative stress. Iron chelation maintained the mitochondrial membrane potential, prevented peroxide-induced elevations in superoxide levels, and preserved ATP levels. Although increased intracellular calcium occurred after oxidative stress to astrocytes, the calcium increase was not necessary for collapse of mitochondrial membrane potential. Indeed, when astrocytes were oxidatively stressed in the absence of extracellular calcium, cell death was enhanced, mitochondrial membrane potential collapsed at an earlier time point, and superoxide levels increased. Addnl., the authors' data do not support opening of the mitochondrial permeability transition pore as part of the mechanism of peroxide-induced oxidative stress of astrocytes. Thus, the increase in intracellular calcium following peroxide exposure does not mediate astrocytic death and may even provide a protective function. Finally, the vulnerability of astrocytes and their mitochondria to oxidative stress correlates more closely with iron

availability than with increased intracellular calcium.
REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:759706 CAPLUS
DOCUMENT NUMBER: 130:105655
TITLE: Role of superoxide in apoptosis induced by growth factor withdrawal
AUTHOR(S): Lieberthal, Wilfred; Triaca, Veronica; Koh, Jason S.; Pagano, Patrick J.; Levine, Jerrold S.
CORPORATE SOURCE: Department of Medicine, Boston University Medical Center, Boston, MA, 02118, USA
SOURCE: American Journal of Physiology (1998), 275(5, Pt. 2), F691-F702
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have examined the role of reactive oxygen species (ROS) in apoptosis induced by growth factor deprivation in primary cultures of mouse proximal tubular (MPT) cells. When confluent monolayers of MPT cells are deprived of all growth factors, the cells die by apoptosis over a 10- and 14-day period. Both epidermal growth factor (EGF) and high-dose insulin directly inhibit apoptosis of MPT cells deprived of growth factors. Growth factor deprivation results in an increase in the cellular levels of superoxide anion while apoptosis of MPT cells induced by growth factor withdrawal is inhibited by a number of antioxidants and scavengers of ROS. Growth factor deprivation also results in activation of caspase activity, which is inhibited by EGF and high-dose insulin as well as by the ROS scavengers and antioxidants that inhibit apoptosis. The cell-permeant caspase inhibitor, z-Val-Ala-Asp-CH2F (zVAD-fmk), prevents the increase in caspase activity and markedly inhibits apoptosis induced by growth factor deprivation. However, zVAD-fmk had no effect on the increased levels of superoxide associated with growth factor deprivation. Thus, we provide novel evidence that ROS play an important role in mediating apoptosis associated with growth factor deprivation. ROS appear to act upstream of caspases in the apoptotic pathway. We hypothesize that oxidant stress, induced by growth factor withdrawal, represents a signaling mechanism for the default pathway of apoptosis.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:511732 CAPLUS
DOCUMENT NUMBER: 129:258448
TITLE: Mitochondrial dysfunction in neurodegenerative diseases
AUTHOR(S): Beal, M. Flint
CORPORATE SOURCE: Neurology Service/WRN 408, Massachusetts General Hospital and Harvard Medical School, Boston, MA, 02114, USA
SOURCE: Biochimica et Biophysica Acta, Bioenergetics (1998), 1366(1-2), 211-223
CODEN: BBBEB4; ISSN: 0005-2728
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 125 refs. A potential pivotal role for mitochondrial dysfunction in neurodegenerative diseases is gaining increasing acceptance. Mitochondrial dysfunction leads to a number of deleterious

consequences including impaired calcium buffering, generation of free radicals, activation of the mitochondrial permeability transition and secondary excitotoxicity. Neurodegenerative diseases of widely disparate genetic etiologies may share mitochondrial dysfunction as a final common pathway. Recent studies using cybrid cell lines suggest that sporadic Alzheimer's disease is associated with a deficiency of cytochrome oxidase. Friedreich's ataxia is caused by an expanded GAA repeat resulting in dysfunction of frataxin, a nuclear encoded mitochondrial protein involved in mitochondrial iron transport. This results in increased mitochondrial iron and oxidative damage. Familial amyotrophic lateral sclerosis is associated with point mutations in superoxide dismutase, which may lead to increased generation of free radicals and thereby contribute to mitochondrial dysfunction. Huntington's disease (HD) is caused by an expanded CAG repeat in an unknown protein termed huntingtin. The means by which this leads to energy impairment is unclear, however studies in both HD patients and a transgenic mouse model show evidence of bioenergetic defects. Mitochondrial dysfunction leads to oxidative damage which is well documented in several neurodegenerative diseases. Therapeutic approaches include methods to buffer intracellular ATP and to scavenge free radicals.

REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:511727 CAPLUS

DOCUMENT NUMBER: 129:242849

TITLE: Mitochondrial control of apoptosis: the role of cytochrome c

AUTHOR(S): Cai, Jiyang; Yang, Jie; Jones, Dean P.

CORPORATE SOURCE: Department of Biochemistry, Emory University, Atlanta, GA, 30322, USA

SOURCE: Biochimica et Biophysica Acta, Bioenergetics (1998), 1366(1-2), 139-149
CODEN: BBBEB4; ISSN: 0005-2728

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 102 refs. Mitochondrial cytochrome c (cyt c) has been found to have dual functions in controlling both cellular energetic metabolism and apoptosis. Through interaction with apoptotic protease-activating factors (Apaf), cyt c can initiate the activation cascade of caspases once it is released into the cytosol. The loss of a component of the mitochondrial electron transport chain also triggers the generation of superoxide. Although cyt c can be released independent of the mitochondrial permeability transition (MPT), the accompanying cellular redox change can trigger the MPT. Since another apoptotic protease, AIF, is released by MPT, the 2 sep. pathways provide redundancy that ensures effective execution of the cell death program. Anti-apoptotic Bcl-2 family proteins function as gatekeepers to prevent the release of both cyt c and AIF. In spite of their stabilization effect on the mitochondrial outer membrane, Bcl-2 proteins may also be involved in the direct binding of Apaf mols. as regulatory elements further downstream from the mitochondrial apoptotic signals.

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:678460 CAPLUS

DOCUMENT NUMBER: 127:344393
TITLE: The apoptosis-necrosis paradox. Apoptogenic proteases activated after mitochondrial permeability transition determine the mode of cell death
AUTHOR(S): Hirsch, Tamara; Marchetti, Philippe; Susin, Santos A.; Dallaporta, Bruno; Zamzami, Naoufal; Marzo, Isabel; Geuskens, Maurice; Kroemer, Guido
CORPORATE SOURCE: Unite Propre de Recherche 420, Centre National de la Recherche Scientifique, Villejuif, F-94801, Fr.
SOURCE: Oncogene (1997), 15(13), 1573-1581
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mitochondrial alterations including permeability transition (PT) constitute critical events of the apoptotic cascade and are under the control of Bcl-2 related gene products. Here, we show that induction of PT is sufficient to activate CPP32-like proteases with DEVDase activity and the associated cleavage of the nuclear DEVDase substrate poly(ADP-ribose) polymerase (PARP). Thus, direct intervention on mitochondria using a ligand of the mitochondrial benzodiazepin receptor or a protonophore causes DEVDase activation. In addition, the DEVDase activation triggered by conventional apoptosis inducers (glucocorticoids or topoisomerase inhibitors) is prevented by inhibitors of PT. The protease inhibitor N-benzyloxycabonyl-Val-Ala-Asp-fluoromethylketone (Z-VAD.fmk) completely prevented the activation of DEVDase and PARP cleavage, as well as the manifestation of nuclear apoptosis (chromatin condensation, DNA fragmentation, hypoploidy). In addition, Z-VAD.fmk delayed the manifestation of apoptosis-associated changes in cellular redox potentials (hypergeneration of superoxide anion, oxidation of compds. of the inner mitochondrial membrane, depletion of non-oxidized glutathione), as well as the exposure of phosphatidylserine residues in the outer plasma membrane leaflet. Although Z-VAD.fmk retards cytolysis, it is incapable of preventing disruption of the plasma membrane during protracted cell culture (12-24 h), even in conditions in which it completely blocks nuclear apoptosis (chromatin condensation and DNA fragmentation). Electron microscopic anal. confirms that cells treated with PT inducers alone undergo apoptosis, whereas cells kept in identical conditions in the presence of Z-VAD.fmk die from necrosis. These observations are compatible with the hypothesis that PT would be a rate limiting step in both the apoptotic and the necrotic modes of cell death. In contrast, it would be the availability of apoptogenic proteases that would determine the choice between the two death modalities.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:692924 CAPLUS
DOCUMENT NUMBER: 126:155668
TITLE: Why are mitochondria involved in apoptosis?. Permeability transition pores and apoptosis as selective mechanisms to eliminate superoxide -producing mitochondria and cell
AUTHOR(S): Skulachev, Vladimir P.
CORPORATE SOURCE: Department of Bioenergetics, A.N. Belozersky Institute of Physico-Chemical Biology, Moscow State University, Moscow, 119899, Russia
SOURCE: FEBS Letters (1996), 397(1), 7-10
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

LANGUAGE: English

AB In the preceding paper [Petit et al. (1996) FEBS Lett., in press], Petit and co-authors summarize recent results of their studies on the involvement of mitochondria in apoptosis. The mechanism consists in the release to the cytosol of a protein (presumably a protease) that is normally sequestered in the intermembrane space of mitochondria. This protein, when added to isolated nuclei, caused typical apoptotic changes. Its release from mitochondria was shown to occur as a result of disruption of the outer mitochondrial membrane due to swelling of mitochondria caused by opening of so-called permeability transition pores in their inner membranes. Increase in the level of products of the one-electron reduction of O2 (reactive oxygen species, ROS) is known to induce the mitochondrial pores. The hypothesis described here assumes that pore formation and apoptosis are involved in the organization of a defense system preventing ROS formation. It is proposed that ROS-induced pore opening lowers ROS production due to (a) maximal stimulation of mitochondrial O2 consumption and, hence, intracellular [O2] lowering and (b) complete dissipation of mitochondrial membrane potentials and, as a consequence, maximal oxidation of such respiratory chain carriers as CoQ·- which serve as one-electron O2 reductants. ROS decrease allows pore closure. If, nevertheless, ROS are still accumulating in a mitochondrion, long-lived pores cause degradation of the organelle which cannot import and synthesize proteins due to the absence of the membrane potential. In this way, ROS-producing mitochondria can be eliminated (mitochondrial selection). Another result of the long-lived pores is mitochondrial swelling. This disrupts the outer mitochondrial membrane and releases the apoptosis-inducing protein. Apoptosis eliminates ROS-producing cells (cell selection).

L4 ANSWER 19 OF 19 MEDLINE on STN

ACCESSION NUMBER: 2001362766 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11421613
TITLE: Intestinal mitochondrial dysfunction in surgical stress.
AUTHOR: Ramachandran A; Patra S; Balasubramanian K A
CORPORATE SOURCE: Department of Gastrointestinal Sciences, The Wellcome Trust Research Laboratory, Christian Medical College & Hospital, Vellore, 632004, India.
SOURCE: The Journal of surgical research, (2001 Jul) Vol. 99, No. 1, pp. 120-8.
Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 6 Aug 2001
Last Updated on STN: 6 Aug 2001
Entered Medline: 2 Aug 2001

AB BACKGROUND: Surgical stress is associated with altered intestinal function. Our earlier study using a rat model indicated that oxidative stress plays an important role in this process. Since mitochondria are crucial to cellular function and survival and are both a target as well as a source of reactive oxygen species, the present study looks at the changes in enterocyte mitochondria during surgical stress. METHODS: Surgical stress was induced by opening the abdominal wall and handling the intestine as done during laparotomy. Mitochondria were prepared from the isolated enterocytes at different time periods after surgical stress. The effect of surgical stress on enterocyte mitochondrial ultrastructure, respiration, anti-oxidant enzyme activity, thiol redox status, calcium flux, permeability, and matrix enzymes was then studied. RESULTS: Surgical stress resulted in alterations in mitochondrial respiration and

thiol redox status. It was also associated with altered mitochondrial matrix enzyme activity, decreased superoxide dismutase activity, induction of mitochondrial permeability
transition, and swelling, as well as impairment of mitochondrial calcium flux. These alterations were seen at a maximum of 60 min following surgical stress and were reversed by 24 h. CONCLUSIONS: Laparotomy and mild intestinal handling itself results in enterocyte mitochondrial damage. Since mitochondria are important cellular organelles, this damage can probably lead to compromised intestinal function.

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